Modeling anorexia nervosa: transcriptional insights from human iPSC-derived neurons.

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Public Summary:
Anorexia nervosa is the psychiatric disorders that kills most people in the world. The biological basis of this condition is unknown and there is lots of stigma surrounding it. To understand and define better what there the molecular and cellular mechanisms related to Anorexia, we use cellular tools from this CIRM grant to reproduce neurons derived from affected people and non-affected controls in the laboratory. When we carefully compare them, we found that a gene called TACR1 is very active on the disease neurons. This gene regulates the gut-brain axis and is involved on the perception of "body fat" by the brain. Thus, we uncovered a highly significant molecular mechanism that help us to explain the clinical symptoms and to design pharmacological interventions using this pathway.

Scientific Abstract:
Anorexia nervosa (AN) is a complex and multifactorial disorder occurring predominantly in women. Despite having the highest mortality among psychiatric conditions, it still lacks robust and effective treatment. Disorders such as AN are most likely syndromes with multiple genetic contributions, however, genome-wide studies have been underpowered to reveal associations with this uncommon illness. Here, we generated induced pluripotent stem cells (iPSCs) from adolescent females with AN and unaffected controls. These iPSCs were differentiated into neural cultures and subjected to extensive transcriptome analysis. Within a small cohort of patients who presented for treatment, we identified a novel gene that appears to contribute to AN pathophysiology, TACR1 (tachykinin 1 receptor). The participation of tachykinins in a variety of biological processes and their interactions with other neurotransmitters suggest novel mechanisms for how a disrupted tachykinin system might contribute to AN symptoms. Although TACR1 has been associated with psychiatric conditions, especially anxiety disorders, we believe this report is its first association with AN. Moreover, our human iPSC approach is a proof-of-concept that AN can be modeled in vitro with a full human genetic complement, and represents a new tool for understanding the elusive molecular and cellular mechanisms underlying the disease.